Remarks

Examination of Unelected Species

Applicants understand that the claims have been examined with respect to the following species: protease nexin-2 as the heparin binding domain in claims 8 and 22, SEQ ID NO:10 in claims 9 and 23, and SEQ ID NO:12 as the second amino acid sequence in claim 15. It is not clear from the first paragraph on page 2 of the Office Action, however, whether the other species recited in claims 8, 9, 15, 22, and 23 already have been examined or whether they will be examined in the next Office Action. Applicants respectfully request clarification of the status of the non-elected species.

The Amendments

Claim 1 has been amended to recite that the chimeric protein comprises "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or c) a Kunitz-type domain 2 of TFPI-2 or a mutein thereof and (d) a Kunitz-type domain 1 of TFPI or a mutein thereof." This recitation is supported *inter alia* by originally filed claim 2.

Claim 2 has been amended to replace the recitation "molecule" in the last line with "chimeric protein," which has antecedent basis in claim 2.

The definitions of K_1 and K_2 in claim 16 have been rewritten for clarity and are supported by the original language of the claim.

New claim 88 is supported by originally filed claim 2.

None of these amendments adds new matter or requires a new search.

Objections to the Specification and Claims

The Office Action objects to the use of brackets in the specification and in claims 10, 11, 16-18, 24, and 25 because the use of the brackets is allegedly improper. Applicants know of no rule that prohibits the use of brackets in a patent. In fact, related U.S. Patents 6,174,721 and 5,589,359 have the same disclosure as the present specification and were printed using brackets in the same places as in the present specification.

The Office Action also objects to the use of brackets as confusing, because brackets are commonly used to indicate subject matter to be deleted. Use of brackets only indicates subject matter to be deleted, however, if a specific instruction is made to delete that subject matter. No specific instruction has been made to delete the bracketed subject matter in the specification or claims. Subject matter to be deleted from the claims amended in this paper is indicated using a double strikethrough.

Applicants respectfully request withdrawal of the objections.

The Obviousness-Type Double Patenting Rejections

Claims 1-12, 16-25, and 73 stand rejected as obvious over claims 1-17 of U.S. Patent 6,174,721. Claims 1-12, 16-27, and 73 stand rejected as obvious over claims 1-24 of U.S. Patent 5,589,359.

Upon an indication of allowability of the pending claims but for the issue of obviousness-type double patenting, Applicants will consider filing a Terminal Disclaimer.

The Rejection of Claims 2-25 Under 35 U.S.C. § 112, second paragraph

Claims 2-25 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse the rejection.

The recitations "wherein a, b are integers from 0-6" and "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences or non-native sequence" are said to render claims 2-13 indefinite because when A=B=C=0 and a=b=0, the length of the chimeric protein is zero. Claims 2-13 ultimately depend from claim 1. The chimeric protein recited in claim 1 comprises "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof ***and*** (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or (c) a Kunitz-type domain 2 of TFPI-2 or a mutein thereof ***and*** (d) a Kunitz-type domain 1 of TFPI or a mutein thereof" (emphasis added). Thus, the chimeric proteins recited in dependent claims 2-13 must also comprise "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof ***and*** (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or (c) a Kunitz-type domain 2 of TFPI-2 or a mutein thereof ***and*** (d) a Kunitz-type domain 1 of TFPI or a mutein thereof." Dependence on claim 1 precludes the combination A=B=C=0 and a=b=0. Thus, claims 2-13 are definite.

The Office Action also questions which portions of native TFPI or TFPI-2 sequences or non-native sequence are intended by the recitation "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences or non-native sequence." The recitation is open to inclusion of any native TFPI or TFPI-2 sequences or any sequences that are not part of a native TFPI or TFPI-2 sequence.

Claims 2-13 also are said to be indefinite because their recitation of muteins does not further limit claim 1. Muteins are recited in claim 1; claim 2 is a proper dependent claim

because it recites a generic formula not recited in claim 1; claims 3-13 also incorporate the generic formula and thus also are proper dependent claims.

Dependent claims 14 and 15 are said to be indefinite because SEQ ID NO:19 contains "a mutated Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI." Claim 14 has been amended to be in independent form. Claim 15 has been amended to depend from claim 14.

Dependent claims 16-25 are said to be indefinite because claim 16 recites a mutein of Kunitz-type domain 1 or 2 or TFPI or TFPI-2 and does not further limit claim 1. As amended, claim 1 recites "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or (c) a Kunitz-type domain 2 of TFPI-2 or a mutein thereof and (d) a Kunitz-type domain 1 of TFPI or a mutein thereof." With this amendment to claim 1, claims 16-25 are a proper dependent claims.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 2-13 and 16-25 Under 35 U.S.C. § 112, first paragraph

Claims 2-13 and 16-25 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled for their full scope. Applicants respectfully traverse the rejection.

There are two bases for the rejection. First, the Office Action states that when if A=B=C=0 and a=b=0 in the generic formula of claim 2, the length of the chimeric protein is zero, and the specification does not enable such a protein. As explained above with respect to the rejection of claims 2-13 under 35 U.S.C. § 112, second paragraph, the chimeric protein recited in claim 2 includes "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof ***and*** (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or (c) a Kunitz-type domain 2 of TFPI-2 or a

mutein thereof ***and*** (d) a Kunitz-type domain 1 of TFPI or a mutein thereof," as recited in claim 1. Dependence on claim 1 precludes the combination A=B=C=0 and a=b=0, which moots this basis of the rejection.

Second, the Office Action asserts that the specification does not enable chimeric proteins containing muteins of the recited Kunitz domains. Because amended claim 1 now also recites muteins, Applicants assume this basis for the rejection now also applies to claims 1, 26, 27, and 73.

To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the present specification must teach one of skill in the relevant art how to make and use chimeric proteins comprising a mutein of a Kunitz-type domain 1 or 2 of TFPI or TFPI-2 without the need for undue experimentation. *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). The scope of enablement in the specification must bear a reasonable correlation to the scope of the recited genera of muteins. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970). The present specification meets this standard.

The Office Action acknowledges only one mutein taught in the specification (*i.e.*, the mutein in which the lysine residue in the P_1 reactive site of the first Kunitz-type domain of TFPI (SEQ ID NO: 1) is replaced with arginine). The specification, however, teaches numerous other examples of TFPI and TFPI-2 muteins:

> Factor VIIa/TF/Xa binding proteins of the invention include muteins of TFPI and TFPI-2, the muteins having single or multiple amino acid substitutions. Muteins within the scope of this definition include: (a) TFPI or TFPI-2 muteins having 1-5 conservative amino acid substitutions that do not substantially change the conformation of the molecule; (b) TFPI or TFPI-2 muteins with amino acid substitutions that eliminate one or more of the three sites for N-linked glycosylation; (c) TFPI muteins

having 1-5 amino acid substitutions that change a residue of TFPI to a corresponding residue of TFPI-2; (d) TFPI-2 muteins having 1-5 amino acid substitutions that change a residue of TFPI-2 to a corresponding residue of TFPI; (e) TFPI or TFPI-2 muteins with amino acid substitutions in P_1 reactive sites in one or more Kunitz-type domains; and (f) TFPI or TFPI-2 muteins with amino acid substitutions at positions within 5 amino acids of the P_1 reactive sites in one or more Kunitz-type domains. In a preferred embodiment, the lysine residue in the P_1 -reactive site of the first Kunitz-type domain of TFPI (SEQ ID NO: 1) is replaced with arginine.

* * *

The muteins of TFPI and TFPI-2 may also be truncated at the end of the second Kunitz-type domain. Such truncated molecules retain the ability to bind factor VIIa/TF complex and Xa yet can be expressed at higher levels in such organisms as yeast. The truncated TFPI and TFPI-2 muteins will likely lead to enhanced recovery of a product containing correctly folded Kunitz-type domains due to the removal of six cysteine residues in the third Kunitz-type domain. The truncated muteins may also have the tail sequence of TFPI or of TFPI-2 attached at the carboxy-terminal end to give the mutein cell surface-binding ability, preferably by binding to glycosaminoglycans (including heparin) or phospholipid at the cell surface.

Page 8, line 19, to page 9, line 3; page 10, lines 5-12. The amino acid sequences of TFPI and TFPI-2 were known in the art when this application was filed, as were the Kunitz-type domains, N-linked glycosylation sites, and P_1 reactive sites of TFPI and TFPI-2. See page 1, line 10, to page 2, line 26 of the specification. Thus, in addition to the single mutein acknowledged in the Office Action, the specification teaches a wide variety of other muteins that can be used in the recited chimeric proteins.

The specification also teaches how to make the disclosed muteins:

Muteins of TFPI and TFPI-2 containing one or more amino acid substitutions may be prepared by appropriate mutagenesis of the sequence of a recombinant cloning vehicle encoding TFPI or

> TFPI-2, using techniques known to those skilled in the art. Techniques for mutagenesis include, without limitation, site specific mutagenesis. Site specific mutagenesis can be carried out using any number of procedures known in the art. These techniques are described by Smith, Annual Review of Genetics, 19:423 (1985), and modifications of some of the techniques are described in Methods in Enzymology, 154, part E, (eds.) Wu and Grossman (1987), chapters 17, 18, 19, and 20. A preferred procedure when using site specific mutagenesis is a modification of the Gapped Duplex site directed mutagenesis method. The general procedure is described by Kramer, et al., in chapter 17 of the Methods in Enzymology, above. Another technique for generating point mutations in a nucleic acid sequence is the use of PCR techniques, including overlapping PCR, as described in PCR PROTOCOLS: A GUIDE TO METHODS AND APPLICATIONS, (eds.) Innis, Gelfand, Sninsky and White (Academic Press, 1990).

Page 9, line 22 to page 10, line 4.

The teachings of the specification quoted above bear a reasonable correlation to the scope of the recited genera of muteins of Kunitz-type domains 1 and 2 of TFPI or TFPI-2. Provided with these teachings, one skilled in the art would be able to make and use chimeric proteins comprising muteins of Kunitz-type domains 1 or 2 of TFPI or TFPI-2 without undue experimentation.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claim 2 Under 35 U.S.C. § 102(b)

Claim 2 stands rejected under 35 U.S.C. § 102(b) as anticipated by Voet *et al.*, Biochemistry, pages 59-63 ("Voet"). Voet is cited as teaching single amino acids, which fall within the scope of the generic formula recited in claim 2 if A, a, b, and C are zero and B is 1. Applicants respectfully traverse the rejection.

A printed publication that antedates an invention under 35 U.S.C. § 102 must disclose each element of the invention. *Kalman v. Kimberly-Clark Corp.*, 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As explained above, because claim 2 depends from claim 1, the chimeric protein of claim 2 must include "(a) a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and (b) a Kunitz-type domain 2 of TFPI or a mutein thereof; or (c) a Kunitz-type domain 2 of TFPI-2 or a mutein thereof and (d) a Kunitz-type domain 1 of TFPI or a mutein thereof." Voet does not disclose such a chimeric protein. Thus, Voet does not anticipate claim 2.

Applicants respectfully request withdrawal of the rejection.

Please continue to address correspondence to Joseph H. Guth, Esq., Reg. No. 31,261, Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

BANNER & WITCOFF, Ltd.

Date: February 27, 2003

By: Lisa M. Hemmendinger

Lisa M. Hemmendinger
Registration No. 42,653

1001 G Street, NW
Washington, DC 20001
202-508-9100